IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Haim AVIV et al.	Confirmation No.:	6729
Application No.:	10/644,687	Group Art Unit:	1626
Filed:	August 19, 2003	Examiner:	T.A. Solola
For:	HIGH ENANTIOMERIC PURITY DEXANABINOL FOR PHARMACEUTICAL COMPOSITIONS	Attorney Docket No.:	87754-7500

DECLARATION OF RAPHAEL MECHOULAM UNDER 37 C.F.R. § 1.132

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I am a co-inventor, together with Jeffery J. Feigenbaum, Naftali Lander and Morris Srebnik, of U.S. Patent No. 4,876,276 which claims the compound HU-211, the full chemical name of which is 1,1-dimethylheptyl-(3*S*,4*S*)-7- hydroxy-delta^6-tetrahydrocannabinol, subsequently assigned the trivial chemical name dexanabinol. I am a citizen of Israel and currently reside at 12 Tchernihovsky Street , Jerusalem 92581, Israel.

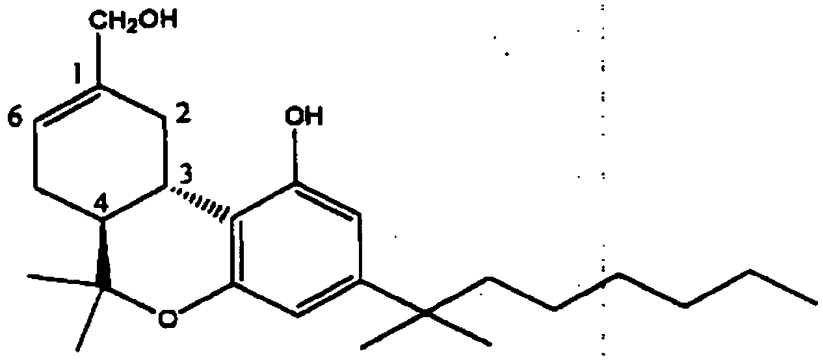
2. I received my Ph.D. degree from the Weizmann Institute of Science, Rehovot, Israel, in 1958. I have worked in research in the Hebrew University of Jerusalem since 1966. I was a full professor in the School of Pharmacy of the Hebrew University of Jerusalem from 1972, until I retired in 2003. As a professor emeritus, I continue to do research at the Hebrew University.

3. I was the Lionel Jacobson Professor of Medicinal Chemistry at the Hebrew University of Jerusalem, for almost thirty years. I have over forty years of experience in the research, synthesis, testing, and development of new compounds, compositions, and methods of making and using the same. Since the beginning of my career, I have published almost 300 scientific articles in highly regarded journals and books, and

have presented my achievements at many international scientific conferences. Most of these publications deal with chemistry, pharmacology and clinical effects of plant, synthetic and mammalian cannabinoids. I was the first to identify the psychotropically active constituent in marijuana (delta-9-tetrahydrocannabinol) as well as the first active endocannabinoid in brain (anandamide). I am a member of several scientific societies and was elected a member of the Israel Academy of Sciences in 1994. I have received numerous local and international prizes. Attached are my curriculum vitae and list of publications.

4. I have reviewed and understand the above-identified patent application, the pending claims, the Office Action, and the reference cited therein. In particular, I am a co-inventor of U.S. Patent No. 5,284,867 to Kloog et al., a patent that I understand has been cited against the claims of the above-identified application.

5. The above-identified application is directed to a compound, or pharmaceutically acceptable salt, ester, or solvate thereof, having the formula:



having the (3S,4S) configuration and being in enantiomeric excess of at least 99.90% over the (3R,4R) enantiomer. The application further relates to compositions comprising the compound and uses thereof. The above-identified application further provides a large-scale synthetic procedure for the preparation of dexanabinol, HU-211, and a new analytical method for the determination of the amount of the enantiomer HU-210, which allows for the accurate evaluation of the enantiomeric excess of dexanabinol.

6. The Kloog et al. patent does not teach the preparation of HU-211, nor the enantiomeric excess that are currently claimed. Rather, Kloog et al. discloses new uses of previously known compounds in particular of HU-211. The synthesis of HU-211 was

disclosed in U.S. Patent No. 4,876,276, for which I am a co-inventor. In U.S. Patent No. 5,284,867 to Kloog et al., as well as in U.S. Patent No. 4,876,276 to Mechoulam et al. wherein HU-211 is first disclosed, the phraseology used in connection with enantiomeric purity is "essentially free of the (3R,4R) enantiomer", which is defined by the fact that the claimed compounds are devoid of any undesired cannabimimetic psychotropic side effects, at the doses tested.

7. The Examiner asserts that absent of showing to the contrary, the phraseology "essentially free of the (3R,4R) enantiomer" anticipates the present claims wherein the (3S,4S) enantiomer is in enantiomeric excess of at least 99.90% over the (3R,4R) enantiomer. I have been asked to give my opinion regarding the superior enantiomeric purity of the claimed compound in the present application.

8. At the time we filed the application serial number 112,705 relating to dexanabinol, which issued as U.S. Patent No. 4,876,276, the enantiomeric purity was achieved due to crystallinity of intermediate compound V, 4-oxomyrtenyl pivalate. We had no direct analytical method to measure the amount of HU-210 and we were not able to determine mathematically the enantiomeric purity of dexanabinol. The sole assay available at the time was functional and the presence of excess amount of HU-210 was detected using the tetrad assay. This method tests four different parameters in rodents and is designed to monitor cannabimimetic effects in a given preparation. Such an assay does not reveal the degree of absolute purity of the compound nor its enantiomeric excess.

9. In our article entitled "Synthesis of the individual, pharmacologically distinct, enantiomers of a tetrahydrocannabinol derivatives" published in Tetrahedron Assymetry 1(5): 315-318 (1990), we disclosed some information concerning the enantiomeric excess of dexanabinol (HU-211) over its enantiomer HU-210. A copy of this article is attached hereto. We followed a slightly improved synthetic process, as compared to U.S. Patent No. 4,876,276, wherein the desired enantiomer of 4-oxomyrtenyl pivalate was first isolated by chromatography, then crystallized from pentane, and wherein dexanabinol was thrice recrystallized from pentane. After this synthesis, we did not directly assess the amount of HU-211 by reverse phase HPLC and of HU-210 by chiral HPLC, but of their substituted bis (MTPA) esters. There is no certainty that derivatization was of equal efficacy for each of the enantiomer and it is possible that the relative amount of the derivatized

enantiomers does not correlate with the relative amount of the original underivatized enantiomers as accurately assessed using the analytical methods disclosed in the present application. Even if we assume that the enantiomeric excess of 99.8% we reported for the derivatized enantiomers reflected the true enantiomeric excess of the original enantiomers, it is our opinion that the absolute purity of dexanabinol *per se* was below the value of at least 98% and the amount of HU-210 in the preparation was above the value of at least 0.05%. These threshold values, indicated in Table 1 of the present application, were achieved following the synthetic procedures disclosed in the present application.

10. The compound of Kloog et al. does not have an enantiomeric excess of at least 99.9% of the (3S,4S) enantiomer over the (3R,4R) enantiomer, as required by the instant claims. In fact, as we understand, the compound of Kloog et al. is at most as pure as the dexanabinol disclosed in the aforementioned article which, as detailed above, does not disclose a highly pure dexanabinol as required by the present application nor the enantiomeric excess of the unmodified enantiomers.

11. We never synthesized dexanabinol in amounts above laboratory scale, nor have we synthesized pharmaceutical grade dexanabinol intended for human use. We have not developed a synthetic procedure for commercial scale or clinical purposes and have not used during the course of our research analytical methods that directly assessed and quantified the amount of the separate enantiomers. The enantiomeric excess values reported by us, were calculated based on the peak area of the derivatized HU-211 and HU-210, and not as disclosed in the present application based on the standardized calculated amount of each of the underivatized enantiomers.

12. We are aware that the applicant has invested time and resources to improve these initial results by modifying the original procedures. These modifications lead to the development of the current synthetic process and improved analytical methods of the present application, that enable the preparation of dexanabinol of the claimed enantiomeric excess.

13. As one of skill in the art, based on my review of the claimed invention and of the closest prior art, it is my opinion and judgment that the invention as currently claimed provides dexanabinol with superior properties. In particular, the advantage of the

synthetic process, which is adapted to large scale synthesis, and the superiority of the analytical methods, which allow accurate determination of the enantiomeric excess, lead to the preparation of a drug substance appropriate for human use.

14. I further declare that all statements made herein of my knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Dated: March 9, 2005

R. Mechoulam

Printed Name: Raphael Mechoulam
Title: Professor Emeritus of Medicinal Chemistry
at The Hebrew University of Jerusalem

Professor Raphael Mechoulam

1930 Born Sofia, Bulgaria

1952 M.Sc. in Biochemistry, Hebrew University, Jerusalem

1953-56 Army Service

1956-58 Ph.D. studies with Professor F. Sondheimer, Weizmann Institute, Rehovot. Research on steroid synthesis.

1959-60 Postdoctoral research at Rockefeller Institute, New York. Research on the structure of triterpenes.

1960-65 Junior and later Senior Scientist, Weizmann Institute. Resesearch on chemistry of natural products, including cannabinoids, terpenes, alkaloids.

1966- Hebrew University, Jerusalem; 1968 – Associate Professor; 1972 – Professor.

1975- Endowed chair: Lionel Jacobson Professor of Medicinal Chemistry.

1979-82 Rector (Academic Head) of Hebrew University.

1983-85 Pro-Rector, Hebrew University.

1993-94 Visiting Professor, Department of Pharmacology, Medical College of Richmond.

1999-2000 President of the International Cannabinoid Research Society.

Research interests: chemistry and biological activity of natural products and synthetic drugs.

Honors

Somach Sachs Prize for "best research by a scientist below 35 at the Weizmann Institute", 1964.

Distinguished Visiting Professorship, Ohio State University, Columbus, Ohio, 1982-1983.

International Biannual Cannabis meeting (held in Colymbari, Crete), 1990, dedicated to R.M.

"Pharmacology, Biochemistry and Behavior" Nov. 1991 issue dedicated to R.M. for achievements in the cannabinoid field.

Kolthof Prize in Chemistry, 1994, The Technion, Haifa.

Elected, Member Israel Academy of Sciences, 1994.

Hanf prize, Germany, 1997, for "the discovery of THC and lasting research on Cannabis – anandamides".

Hanus Medal, 1998, by Czech Chemical Society in recognition of contribution to cannabinoid chemistry.

David R. Bloom Prize, 1998, for "excellence in pharmaceutical research", Hebrew University.

The International Cannabinoid Research Society (ICRS) establishes an annual award to be named The R. Mechoulam Annual Award in Cannabinoid Research, 1999.

Israel Prize in Exact Sciences – chemistry, 2000.

Ariens Award and Lecture. 2000. Dutch Pharmacological Society sponsored by Solvay Pharmaceuticals. Amsterdam.

Honorary Degree Doctor of Science.
Ohio State University, Columbus, Ohio, 2001.

Elected, Honorary Member of the Israel Society of Physiology and Pharmacology, 2002.

Heinrich Wieland Prize, endowed by Boehringer-Ingelheim, to promote research on "lipids and related substances in the fields of Chemistry, Biochemistry, Physiology, and Clinical Medicine", Germany, 2004.

Name lectures:

Copenhagen, Denmark, 1977, Ferosan Lecture, School of Pharmacy.

Tuscon, Arizona, 1983, Golden Headed Cane Memorial Lecture, Faculty of Medicine.

Stockholm, Sweden, 1994, Ulf von Euler Lecture in Physiology, Karolinska Institute.

Maale Hamisha, 2000, Magnes Memorial Lecture, Israel Society for Physiology and Pharmacology.

R. Mechoulam.

List of publications

Summaries of lectures at scientific meetings are not included.

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2. R. Mechoulam, S. Cohen and A. Kaluszyner. Basic alcoholysis of the trifluoromethyl group in 1,1,1-trifluro-2,2-diarylethenes. J. Org. Chem., 21, 801-802 (1956).

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4. S. Cohen, A. Kaluszyner and R. Mechoulam. On the fluorination of DDT with HF and HgO. J. Amer. Chem. Soc., 79, 5979-5981 (1957).

5. A. Kaluszyner, R. Mechoulam and M. Breuer. Urea and thiourea derivatives for larvidical testing. Bull. Research Council Israel, 7A, 135-137 (1958).

6. E.D. Bergmann, Z.H. Levinson and R. Mechoulam. The toxicity of Veratrum and Solanum alkaloids to housefly larvae. J. Insect Physiol., 2, 162-177 (1958).

7. F. Sondheimer and R. Mechoulam. Further aspects on the Wittig reaction in the steroid series. 20-dehydro-cholesterol. J. Amer. Chem. Soc., 80, 3087-3090 (1958).

8. R. Mechoulam and F. Sondheimer. The Wittig reaction with fluorenone. Formation of cyclopropane derivatives. J. Amer. Chem. Soc., 80, 4386-4388 (1958).

9. F. Sondheimer and R. Mechoulam. The Diels-Alder reaction of steroidal 20-methylene-Δ^{16}-pregnene derivatives with maleic anydride. J. Org. Chem., 24, 106-107 (1959).

10. F. Sondheimer, S. Burstein and R. Mechoulam. Synthesis in the cardiac aglycone field. The conversion of 14α to a 14β hydroxy

group in the androstane series. The ultraviolet spectra of Δ^{15}-androstene-17-ones. J. Amer. Chem. Soc., 82, 3209-3214 (1961).

11. F. Sondheimer, R. Mechoulam and M. Shprecher. 19-Hydroxy-10-isotestosterone. Tetrahedron Letters, 38-44 (1960).

12. R. Mechoulam, F. Sondheimer, A. Melera and F.A. Kincl. The structure of zapotidine. J. Amer. Chem. Soc. 83, 2022 (1961).

13. R. Mechoulam. Stereochemistry of ceanothic (emmolic) acid. Chemistry and Industry, 1835-1836 (1961).

14. R. Mechoulam. The structure of ceanothic acid. J. Org. Chem., 27, 4070-4073 (1962).

15. R. Mechoulam, N. Daniely and Y. Mazur. The structure and synthesis of oleuropeic acid. Tetrahedron Letters, 709-712 (1962).

16. R. Mechoulam and Y. Gaoni. The structure of dihydronicotyrine. Rec. Trav. Chim. Pays-Bas, 82, 1159-1162 (1963).

17. R. Mechoulam and Y. Shvo. The structure of cannabidiol. Tetrahedron, 19, 2073-2078 (1963).

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19. Y. Gaoni and R. Mechoulam. Isolation, structure and partial synthesis of an active constituent of hashish. J. Amer. Chem. Soc., 86, 1646-1647 (1964).

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28. Y. Gaoni and R. Mechoulam. Concerning the isomerization of Δ^1 to Δ^6-tetrahydrocannabinol. J. Amer. Chem. Soc., 88, 5673-5675 (1966).

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37. Y. Gaoni and R. Mechoulam. The iso-tetrahydrocannabinols. Isr. J. Chem., 6, 679-690 (1968).

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49. B. Eckstein, R. Mechoulam and S.H. Burstein. The identification of 5α-androstane-3α, 17β-diol as a major metabolite of pregnenolone in rat overy at the onset of puberty. Nature, 228, 866-868 (1970).

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Two chapters were authored by R. Mechoulam:
a) Cannabinoid Chemistry – R. Mechoulam, pp. 1-99
b) Structure-Activity Relationships in the Cannabinoid Series – R. Mechoulam and H. Edery, pp. 101-136.

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SYNTHESIS OF THE INDIVIDUAL, PHARMACOLOGICALLY DISTINCT, ENANTIOMERS OF A TETRAHYDROCANNABINOL DERIVATIVE

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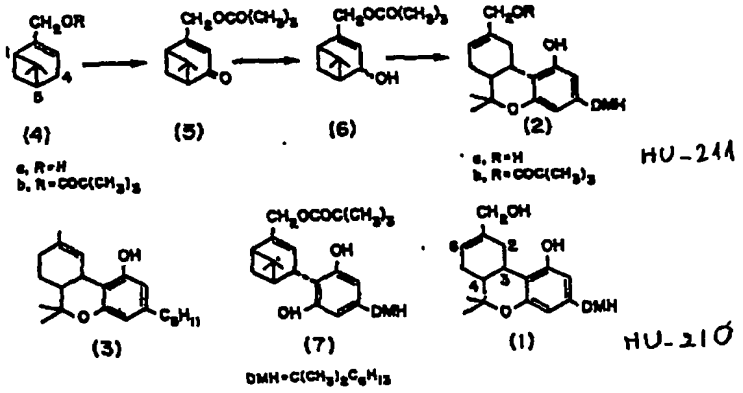
Abstract: The individual enantiomers of the 1,1-dimethylheptyl homolog of 7-hydroxy- Δ^6-tetrahydrocannabinol, (1) and (2a), which exhibit distinct pharmacological profiles, have been obtained with very high e.e. by synthesis from the antipodes of myrtenol.

The 1,1-dimethylheptyl (DMH) homolog of [3R,4R]-7-hydroxy- Δ^6-tetrahydrocannabinol (1) is a very potent psychotropic agent with a hashish type (cannabimimetic) profile of activity. Depending on the animal test used, it is 70-800 times more potent than the natural [3R,4R]- Δ^1-tetrahydrocannabinol ([3R,4R]-Δ^1- THC) (3).[1] By contrast the DMH homolog of [3S,4S]-7-hydroxy-Δ^6-THC (2a) shows practically no cannabimimetic activity (as measured in four different

ee enantiomeric excess.

laboratories) in various animal tests in doses up to several thousand times higher than the ED_{50} of the [3R,4R] enantiomer (1).[1] However (2a) prevents vomitting in pigeons, treated with the strongly emetic anticancer drug cisplatin.[2] It also acts as a functional N-methyl-D-asparate (NMDA) receptor blocker. It binds to sites distinct from those of other non-competitive NMDA antagonists.[3] It is also a potent blocker of NMDA-induced tremor, seizures and lethality in mice,[3] and may therefore prove useful as a drug against NMDA-receptor mediated neurotoxicity. These results indicate that non-cannabimimetic THC-type compounds with [3S,4S] configuration have considerable therapeutic potential.

We report now the synthesis of (1) and (2a). A central aim of our approach was to achieve very high e.e. in order to make possible eventual therapeutic use of the [3S,4S] enantiomer, as the presence of traces of the [3R,4R] enantiomer could lead to undesirable side effects. The synthesis follows an approach previously used by us for the preparation of (3).[4] The few THC-type enantiomeric pairs synthesized so far have not shown high pharmacological stereospecifity;[5] however their e.e. have not been reported, and are presumably not higher than the e.e. of their starting materials (92-98% in the case of α-pinene used in the synthesis of THC).



[1S,5R]-Myrtenol (4a), $[\alpha]_D$ + 47.5 (neat), obtained by oxidation of commercial α-pinene, (Aldrich), $[\alpha]_D$ + 50.7 (neat), was esterfied with pivalyl chloride to the ester (4b) which, on oxidation with anhydrous sodium chromate, at 35°C for 72 hours in acetic acid-acetic anhydride gave, after chromatography on silica gel, 4-oxo-myrtenyl pivalate (5), 30%, m.p. 42-43 (from pentane); $[\alpha]_D$ + 165 ($CHCl_3$); λ max (EtOH) 250 nm (ε 6000); ν max ($CHCl_3$) 1730 and 1670 cm^{-1}; δ ($CDCl_3$) 4.72 (CH_2-O), 5.84 (C=CH). Reduction of (5) with lithium tri-tert-butoxyaluminohydride in dry tetrahydrofuran led to 4-hydroxy-myrtenyl pivalate (6) which, without further purification, was condensed with 5-(1,1-dimethylheptyl)-resorcinol in dry methylene chloride in the presence of boron trifluoride etherate at -20°C. Silica gel chromatography (elution with 10% ether in petroleum ether) gave predominantly the pivalate ester (2b), 50%. Compound (2b) presumably is formed through the intermediate (7), which can be isolated if the condensation reaction is done with p-toluene sulphonic acid, rather than with boron trifluoride etherate. Reduction of (2b) with lithium aluminum hydride led to (2a), 96%, m.p. 141-2°C (from pentane), $[\alpha]_D$ + 227 ($CHCl_3$), δ ($CDCl_3$) 6.40, 6.25 (2 arom H's), 5.6 (C=CH), 4.09 (CH_2-O). The same reaction sequence, starting with commercial [1R,5S]-myrtenol (Aldrich) $[\alpha]_D$ − 57.7 , (neat) gave (1), m.p. 141-2°C, $[\alpha]_D$ -226 ($CHCl_3$). The enantiomeric purity of thrice recrystallized (1) and (2a) was established by h.p.l.c. analysis of the diastereoisomeric bis (MTPA) esters obtained by reaction with (S)-+)-α-methoxy-α-(trifluoromethyl) phenyl-acetyl (MTPA) chloride.[6] The e.e. of (1) and (2a) was found to be higher than 99.8%.[7] This high degree of enantiomeric purity is evidenced also by their distinct binding to a cannabinoid receptor : compound (1) binds with an affinity circa 1500 times higher than the

enantiomeric (2a).[8] The sharply contrasting pharmacologic behavior of (1) and (2a) mentioned above is also indicative of their enantiomeric purity. The high e.e. achieved is probably due to the easy crystallization of the intermediate oxo-esters (5, in the synthesis of 2a) and of the final products (1 and 2a). The Δ^1 isomer of (1) has recently been prepared via a different synthetic route.[9]

The above results show that [3S,4S]-THC-type compounds (such as 2a) can be obtained with very high e.e. and can thus be regarded as promising pharmaceutical entities.[10]

References and Notes

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7. H.p.l.c.: column, 250-4 LiChrospher Si 60 (5 um) cartridge (Merck, Germany); solvent, 95:5 n-hexane:ethyl acetate; flow, 1 ml/min; detector (uv) 270 nm. Bis (MPTA) ester of (1):Rt, 12.5 min; bis (MPTA) ester of (2a):Rt, 15.6 min. N.m.r.:$\delta(CDCl_3)$:bis (MPTA) ester of (1), 3.52, 3.78 (2 OCH_3 groups); bis (MPTA) ester of (2), 3.53, 4.50 (2 OCH_3 groups).
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